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Sarah Wilcox
Printed name of person mailing correspondence

Signature of person mailing correspondence

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Faustman and Hayashi	Confirmation No.:	1044
Serial No.:	10/775,487	Art Unit:	1644
Filed:	February 10, 2004	Examiner:	Skelding, Zachary S.
Customer No.:	21559		
Title:	METHODS FOR DIAGNOSING AND TREATING AUTOIMMUNE DISEASE		

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
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DECLARATION OF DENISE FAUSTMAN, M.D., Ph.D.

I declare:

1. I am a named inventor of the subject matter claimed in United States Patent Application Serial No. 10/775,487, which was filed on February 10, 2004.

2. I am an Associate Professor of Medicine at Harvard Medical School and Director of the Immunobiological Laboratories at the Massachusetts General Hospital. I am also a member of the American Association for the Advancement of Science and co-editor in chief of the Journal of Women's Health. In addition, I am a senior author of over 100 peer-reviewed publications in internationally recognized scientific journals.

3. I have read and understood the Office Action mailed on December 15, 2006. This

Declaration is presented to overcome the rejection of claims 76, 77, 79, and 80 under 35 U.S.C. § 112, first paragraph, for lack of enablement. I have considered the Office's remarks regarding the teachings of the specification with respect to the broad scope of the present claims. In my opinion, these concerns are unwarranted.

4. My co-inventor and I discovered that genetic defects altering NF-κB activity are a common denominator across several autoimmune diseases, including the following: Type I diabetes, lupus, Crohn's disease, Sjogren's syndrome, autoimmune glandular diseases [autoimmune polyendocrinopathy syndrome (APS)-1 or autoimmune polyendorinopathy candidasis ectodermal dystrophy], hypothyroidism, multiple sclerosis, psoriasis, and scleroderma. NF-κB dysregulation has been found not only in humans but in at least two animal models of autoimmune disease. Although the particular modulator of NF-κB activity varies by disease, the diseases remarkably overlap by almost uniformly hampering NF-κB formation or functional activity in ways that are particular to the immune cell type and autoimmune disease. Moreover, we discovered that one result of the genetic defects in NF-κB activity is that the autoreactive immune cells responsible for development of autoimmune diseases are sensitive to exposure to TNF-α, which induces cell death in these cells. Thus, our data confirm that multiple, disparate autoimmune diseases can be treated by administering a TNF-α agonist, such as TNF-α or other TNF-α inducing substance, which promotes cell death in the autoreactive immune cells responsible for, or responsible for exacerbating, the disease condition.

5. The specification provides clear evidence confirming that autoreactive immune cells are sensitive to TNF-α, and thus, that administration of TNF-α to these cells promotes their death. In particular, the present specification discloses that exposure of autoreactive spleen cells from NOD mice, which is an accepted animal model for treatment of type 1 (autoimmune) diabetes mellitus, Sjogren's syndrome, and lupus in humans, fails to promote expression of NFκB (see page 113, line 16, through page 116, line 2; and Figs. 8A-8D), which is normally cytoprotective in these cells. This data is clearly presented in Figures 13A and

13B, which show that autoimmune NOD-male and female T cells die after low dose TNF treatment; a marked change in cell viability can be clearly observed in these cells (see also page 124, lines 20-22; and page 126, line 5, through page 127, line 6). In fact, control T cells from BALB/c mice demonstrate normal viability after exposures to TNF. Thus, TNF-α clearly promotes toxicity in the autoreactive T cells from NOD mice, thereby causing cell death, while the cytotoxic effect of TNF is not observed in non-autoreactive immune cells.

Apoptotic cell death can also be assayed by detecting DNA fragmentation in response to a stimulus. As is clearly shown in Figure 13C of the present application, TNF only induces the death of autoreactive T cells from NOD mice; DNA fragmentation is not observed in T cells from normal BALB/c mice.

6. The methods of the invention have also been validated by researchers working under my direction using autoreactive immune cells obtained from patients having several disparate autoimmune diseases (see Exhibit A). In particular, I have observed that autoreactive T cells obtained from patients diagnosed with Type I diabetes, lupus, scleroderma, Sjogren's syndrome, hypothyroidism, multiple sclerosis, Crohn's disease, and psoriasis are also sensitive to TNF-α agonists, such as TNF-α. Similarly to the autoreactive T cells from NOD mice, autoreactive T cells from patients having these other autoimmune diseases, when exposed to TNF-α, experience cell death. Thus, my data confirms that defects in the NF-κB signaling pathways in autoreactive immune cells is not unique to type I diabetes, but appears to play a role in these other disparate autoimmune diseases.

In culture, I observe that only the specific subpopulation of autoreactive T cells from patients diagnosed with the indicated autoimmune diseases die when exposed to a TNF agonist. I have observed this result in the over 1000 type 1 diabetics studied, and in our studies of greater than 50 patients with lupus, greater than 8 patients with scleroderma, greater than 8 patients with Sjogren's syndrome, greater than 50 patients with hypothyroidism, greater than 20 patients with multiple sclerosis, greater 15 patients with Crohn's disease, and 6 patients with psoriasis. My results confirm that autoreactive immune cells can be distinguished from normal cells by not only defects in NFkB on a molecular level, but also on a cellular level by targeted cell death with TNF agonism, a symptom of the NFkB interruption.

7. I have also confirmed that TNF-α agonists other than TNF-α promote autoreactive immune cell death. I have demonstrated that TNF agonist antibodies promote cell death in autoreactive immune cells from patients having diabetes, lupus, multiple sclerosis, psoriasis, Crohn's, and rheumatoid arthritis (see Exhibit B). Exhibit B, which presents an average of data from experiments performed using cells obtained from patients having each of the indicated autoimmune diseases, clearly shows that even low dose exposure to TNF agonist antibodies results in autoreactive immune cell death.

8. In addition to TNF-α and TNF agonist antibodies, I have further confirmed that other substances that induce endogenous TNF-α expression promote autoreactive immune cell death. For example, BCG, a well known inducer of endogenous TNF, when administered to autoreactive animals with type I diabetes, lupus, or Sjogren's syndrome, successfully delays onset of disease in these animals. Furthermore, a single administration of a TNF inducer to an autoimmune mouse delays for several months the appearance of autoimmune disease in normal mice that receive transfers of autoreactive T cells from the autoimmune mouse (see Exhibit C). This data demonstrates selective autoreactive immune cell elimination by a TNF inducer substance in the same manner as that observed using TNF-α and TNF agonist antibodies.

9. Finally, I note that therapies currently on the market for treatment of rheumatoid arthritis and Crohn's disease are classes of drugs, such as REMICADE® (infliximab), ENBREL® (etanercept), and HUMIRA® (adalimumab), that remove or inactivate serum TNF. As acknowledged by the Examiner (see Office Action, p. 6), the prior art teaches that TNF-α inhibitors are useful in treating human disease, which is contrary to the data presented in the present specification and in this Declaration. To address this paradox, I note that, while anti-TNF therapies certainly can remove inflammation and thus improve the symptoms of autoimmunity, my data and other pre- and post-filing date publications suggest that anti-TNF therapy could exacerbate or elicit new autoimmune disease in some patients. Indeed, neutralization of TNF by drug therapy with anti-TNF has been shown to induce, in some cases,

new or exacerbated autoimmunity (see Exhibit D).

Anti-TNF therapy has been used most broadly in rheumatoid arthritis. In some rheumatic patients, this therapy induces new forms of autoimmunity that mimic multiple sclerosis, autoimmune hemolytic anemia, Type 1 diabetes, lupus, and psoriasis (see, e.g., Bleumink et al., Rheumatology 40:1317-1319, 2001; Cairns et al., Ann. Rheum. Dis. 61:1031-1032, 2002; Charles et al., Arthritis Rheum. 2383-2390, 2000; Feldmann et al., Annu. Rev. Immunol. 14:397-440, 1996; Galaria et al., J. Rheumatol. 27:2041-2044, 2000; Jarrett et al., J. Rheumatol. 30:2287-2291, 2003; Klinkhoff, Drugs 64:1267-1283, 2004; Lipsky et al., N. Engl. J. Med. 343:1594-1602, 2000; Moreland et al., Ann. Intern. Med. 130:478-486, 1999; Shakoor et al., Lancet 359:579-580, 2002; Swale et al., Clin. Exp. Dermatol. 28 :604-607, 2003 ; and Vermeire et al., Gastroenterology 125:32-39, 2003).

The second most common use of anti-TNF therapy is in Crohn's disease. The induction of new autoimmunity has also been observed in these autoimmune patients with this drug therapy. Again, these symptoms can range from new autoantibodies often consistent with lupus to clinical lupus (see, e.g., Sandborn, Acta Gastroenterol. Belg. 64:170-172, 2001; Sandborn and Hanauer, Inflamm. Bowel Dis. 5:119-133, 1999; Schaible, Can. J. Gastroenterol. 14:29C-32C, 2000; and Vermeire et al., Gastroenterology 125:32-39, 2003). Trials were also conducted with anti-TNF therapy in multiple sclerosis patients. In these human studies (see Sandborn, Acta Gastroenterol. Belg. 64:170-172, 2001; Sandborn and Hanauer, Inflamm. Bowel Dis. 5:119-133, 1999; Schaible, Can. J. Gastroenterol. 14:29C-32C, 2000; and Vermeire et al., Gastroenterology 125:32-39, 2003), patients consistently reported disease worsening. In combination with the new onset demyelization, side effects of anti-TNF therapy in both rheumatoid arthritis and Crohn's disease, the data are consistent with some autoimmune patients not benefiting from the removal of TNF (see, e.g., Enayati and Papdakis, J. Clin. Gastroenterol. 39:303-306, 2005; and Thomas et al., Inflamm. Bowel Dis. 10:28-31, 2004).

10. All statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were

made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. § 1001 and that such willful false statements may jeopardize the validity of the application and any patents issued thereon.

6/14/07
Date

Denise Faustman, M.D., Ph.D.

Exhibit A

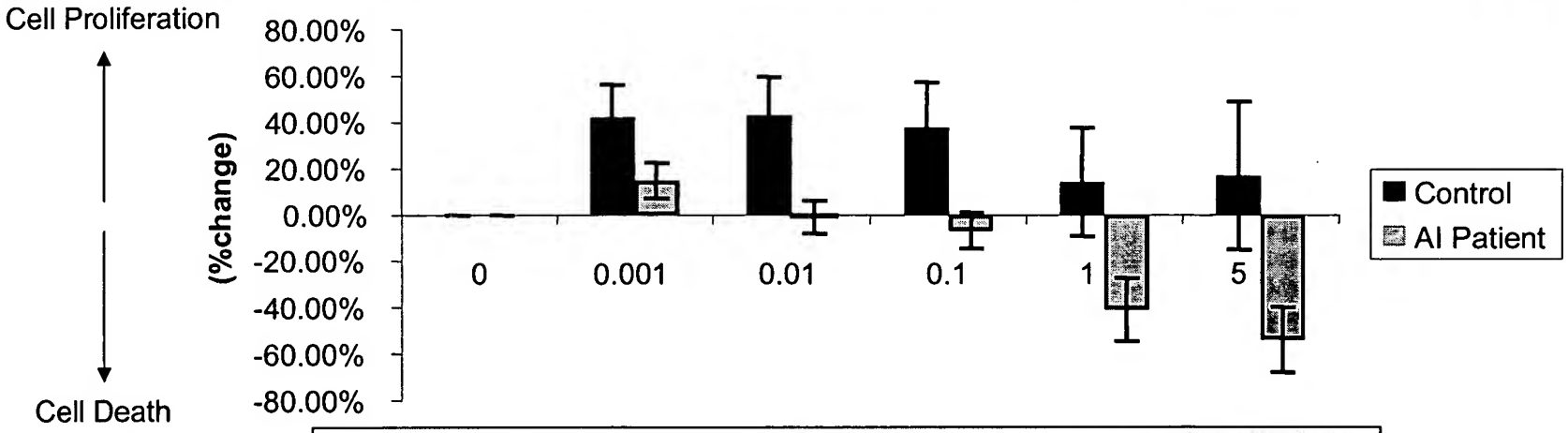
Humans with diverse autoimmune diseases have T cells with TNF induced death:

Verification of NF*k*B interruption

	Autoimmune Samples studied
• Type 1 diabetes	>1000
• Lupus	>50
• Scleroderma	>8
• Sjogren's Syndrome	>8
• Hypothyroidism	>50
• Multiple sclerosis	>20
• Crohn's	>15
• Psoriasis	6

Exhibit B

TNF Agonism Promotes Autoimmune Cell Death

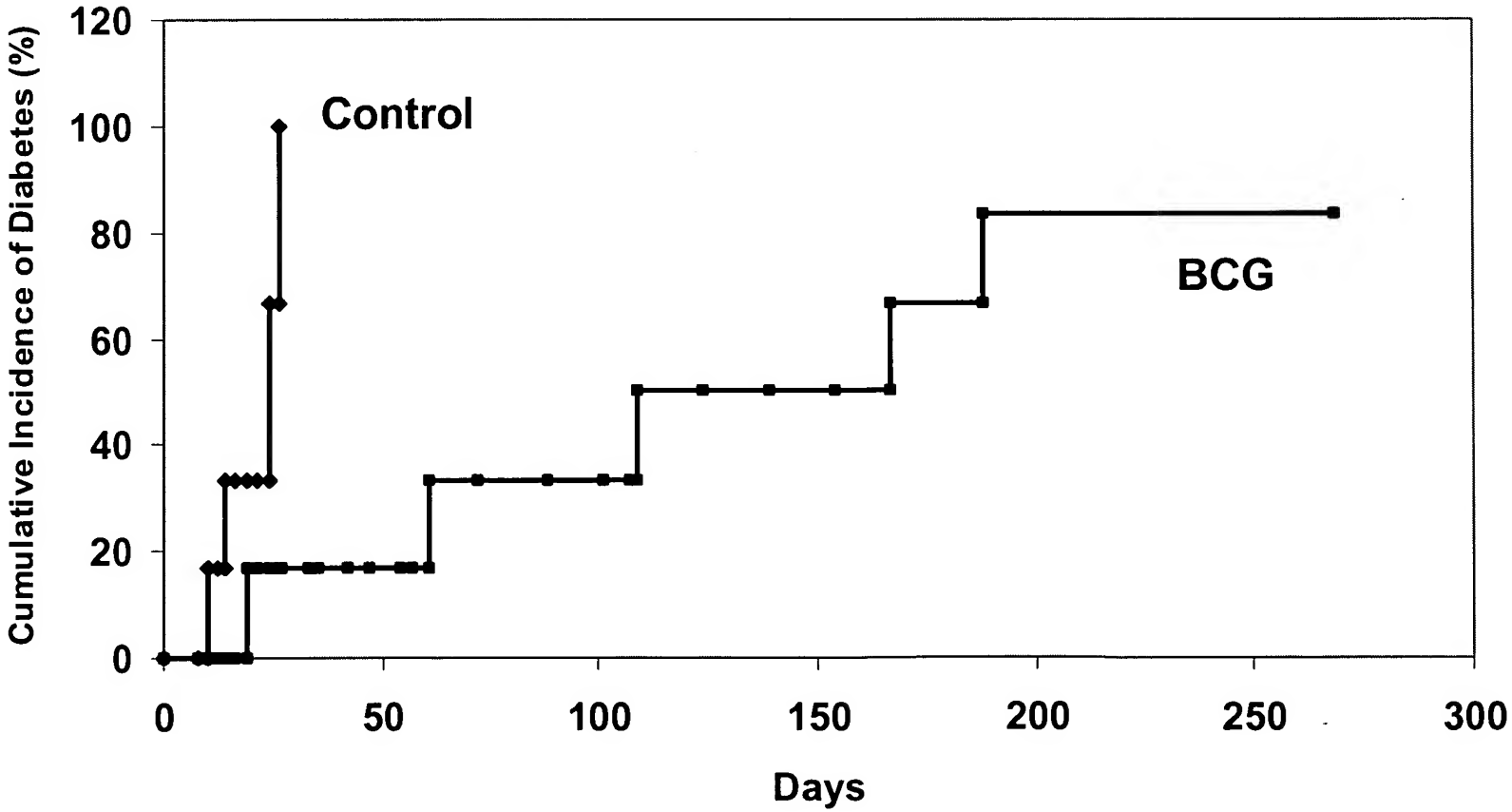


TNF agonist antibody selectively kills autoimmune T cells

T test	
0.001	0.041599
0.01	0.020108
0.1	0.050111
1	0.036054
5	0.025789

Exhibit C

Adoptive cell transfer of autoreactive T cells from an autoimmune mouse treated with BCG significantly delays disease transfer



Untreated autoreactive cell transfers n=12

Autoreactive T cell transfer from BCG treated mouse n=16

Exhibit D *Anti-TNF therapy induces new forms of second-degree autoimmunity*

Second-Degree Complications		
Primary Disease	Autoantibodies	New Autoimmune Disease
Rheumatoid arthritis		Psoriatic skin
		Autoimmune vasulitis
	ANA	
	dsDNA	
Juvenile rheumatoid arthritis		Multiple sclerosis
		Type 1 diabetes
Rheumatoid arthritis and spondylarthropathy	ANA; dsDNA ± nucleosome ± histone	
Colititis		Multiple sclerosis
Crohn's disease	ANA; dsDNA	
		Multiple sclerosis
	ANA	Lupus; autoimmune hemolytic anemia
Sjogren's syndrome	DNA	Autoimmune hepatitis

ANA, anti-nuclear antibodies; dsDNA, double-stranded DNA.

Supplemental Application Data Sheet

Application Information

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Suggested Group Art Unit:	
CD-ROM or CD-R?:	None
Sequence submission?:	None
Computer Readable Form (CRF)?:	No
Number of copies of CRF:	None
Title:	Methods for Diagnosing and Treating Autoimmune Disease
Attorney Docket Number:	~~17633/1124~~ 00786/457003
Request of Early Publication?:	No
Request of Non-Publication?:	No
Suggested Drawing Figure:	Figure 1
Total Drawing Sheets:	35
Small Entity?:	Yes
Petition Included?:	Yes
Secrecy Order in Parent Appl.?:	No

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Domestic Priority Information

Application:	Continuity Type:	Parent Application:	Parent Filing Date:
This Application	Is a Continuation of	09/258,682	02/26/1999
Which is a	Continuation-In-Part of	09/031,629	02/27/1998

Assignee Information

Assignee name: General Hospital Corporation